REMARKS

Claims 70 and 74 have been cancelled. Claims 1, 27, 36, 41, 48, 50, 55, 58, 60, 62, 65, 78 and 80 have been amended to eliminate the recitation of prodrugs and to limit the claims to compounds wherein L is absent with respect to these claims. It is noted that the claims still embrace compounds which are, in fact, prodrugs and this amendment is made without prejudice. Claim 75 has been amended to correct a typographical error in which the substituent L' (leaving group) was indicated as L along with another substituent also labeled as L. The figure as well as the definition was corrected to indicate the leaving group as L'. Claim 34 is amended to correct typographical error. Claim 88 is newly added and corresponds to original Claim 1. Support for the amendment can be found throughout the specification and claims. Claims 1-69 and 75-88 are pending, of which claims 34, 48 and 60 are withdrawn from consideration. No new matter has been introduced by this amendment.

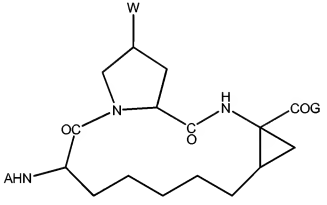
Response to Restriction Requirement/Election

The examiner has reiterated the restriction requirement of the Markush group based on the variable L. The applicants respectfully traverse the restriction requirement.

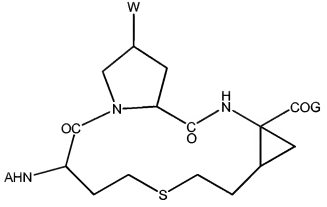
The examiner's restriction is based on the assertion that, "Each ring elemental sequence represents a different core." However, the court in *Ex parte Dahlen and Zwilgmeyer* supports the proposition that there can be variations in a variable in a ring structure that do not support an election/restriction requirement. (42 USPQ 208 1939). The structures I-V herein share several common features including the large ring structure, dipeptide backbone and the proline ring structure. These features together form a core structure that is common to all formulae herein.

In the instant case, the examiner has not provided any reason regarding how applicants' claimed invention ***does not*** (1) share a common utility or (2) share a substantial structural feature even where the variable L is changed. Furthermore, the examiner has not provided any evidence of dissimilar properties among the members of the Markush group justifying restriction.

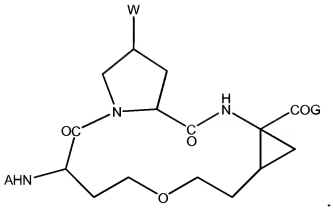
MPEP requires the examination of all species of a claim that recites a Markush group when the alternatives are sufficiently few in number or so closely related search and examination can be made without undue burden. (MPEP 803.02). The Examiner asserts that there is no common core due to the presence of variable L. The direct comparison of the structures of compounds embraced within the various groups is substantial. For example, the following compound falls within elected Group I:



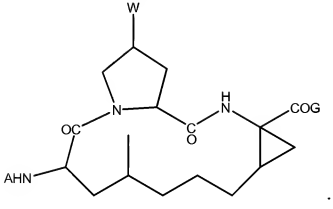
The following compound lies within Group II:



The following compound lies within Group III:



The following compound lies within Group IV:



The compounds of present invention as shown above obviously possess a substantial common core, differing in only one atom or group (CH_2, O, S or $CHCH_3$) and possess a common utility as anti-HCV agents. Such modifications are routinely kept together in a single claim.

In case of restriction of Markush type claims, the invention must be considered as a whole. *In re Harnisch*, 206 USPQ 300, 307 (CCPA 1980). "In determining the propriety of a Markush or Genus grouping the compounds must be considered as wholes and not broken down into elements or other components." *In re Harnisch*, 206 USPQ 300, 307 (CCPA 1980), citing *In re Jones,* 74 U.S. P.Q 149 (CCPA 1947). The court in *In re Harnisch*, requires the consideration of the invention as a whole rather than

focusing on the broken down elements as in this case where the restriction ignores the substantial common structural core between compounds of formulae I-V. The species encompassed by formulae with variable L have the common activity against HCV infection as well as the common structural core resulting in common properties as outlined in *In re Harnisch.* In Harnisch, the court reversed a rejection of a claim to a group of coumarin compounds, stating that the compounds were structurally similar and functionally similar because all were dyestuffs, a classification which was determined to not be repugnant to scientific classification. Like in Harnisch, all of the compounds of the present application share a common core structure and are functionally similar (i.e. they all have anti-HCV activity). The fact that the formula has variables (even within a ring) does not destroy the fact that a common core exists. As such, the applicants respectfully request the withdrawal of the restriction requirement.

"An applicant is given, by the statute, the right to claim his invention with the limitations he regards as necessary to circumscribe the invention, with the proviso that the application comply with the requirements of §112." (*Ex Parte Brouard et. al.,* 201 USPQ 538). The court in *In re Weber, Soder, and Boksay* noted that, "If an application submits a number of claims, it may be dispersed to a number of applications.... If, however, a single claim is divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the sub-genera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification." (198 USPQ 328, 331, CCPA 1978). Thus, the improper imposition of the restriction requirement is contrary to the applicants' statutory right to claim their invention as they see fit, and is clearly contrary to the law as stated in the Weber case. Furthermore, *Ex parte Dahlen and Zwilgmeyer* supports the proposition that there can be variations in a variable in a ring structure that do not support an election/restriction requirement. (42 USPQ 208 1939). Applicants respectfully request the withdrawal of the restriction requirement.

The examiner dismisses the traversal, pointing to other variables, unrelated to the restriction requirement, within the claim. The fact that the claim has a plurality of variables, other than the one relied upon to support the restriction, is not relevant to whether the restriction is proper. Where, as here, compounds within the claim have a significant common core, as plainly illustrated above, does not justify restriction.

The examiner further asserts that each macrocyclic ring system in of itself represents a different core. The examiner, however, supplies no support for the proposition that variability within a ring justifies ignoring the common elements within that ring. Reviewing the art of record speaks against this conclusion. Variability within the ring system is common. While there is variability along the linker that closes the tripeptide backbone, there is, inarguably, a substantial common core structure in the tripeptide backbone.

Response to Claim Objections

The examiner objected to claims 1, 36, 41, 50, 55, 62, 78 and 80 for the informality of including non-elected subject matter. These claims have been amended to limit the claims to the elected subject matter to avoid the objection. However, claim 88 has been introduced and is not so limited, pending final resolution of the restriction requirement. The nonelected claims have been amended to depend from new claim 88.

The examiner has objected to claims 33-35, 46-49 and 58-61 for not ending in a period. Applicants' review of the claim set found claims 34-35, 46-49 and 59-61 to have a period at the end of the sentence, within the last entry in the table. Claims 33 and 58 were amended to provide a period at the end of the sentence. The applicants would like to thank the examiner for pointing out the defects and respectfully request withdrawal of the objection.

Claims Rejections – 35 U.S.C. §112, First Paragraph

Claims 1-33, 35-47, 49-59, 61-70 and 74-87 have been rejected under 35 U.S.C. § 112, first paragraph for the lack of enablement for the prodrug of formula I. Although

the applicants respectfully disagree with the examiner's rejection, in an effort to expedite the allowance of this case, claims 1, 27, 36, 41, 50, 55, 62, 65, 78 and 80 have been amended to delete the term "prodrug". It is noted however, that the claims still embrace compounds which will act as prodrugs, in spite of this amendment. This amendment shall not be viewed as a disclaimer of prodrugs, irrespective of the chemical structure. As such, the rejection under section 112, first paragraph is believed to be moot and the withdrawal of the rejection is respectfully requested.

Claims 66-70 are further rejected under section 112, first paragraph for the lack of enabling disclosure for *in vivo* inhibition of proteases. The examiner notes that the instant application is enabled for the *in vitro* inhibition of NS4 or NS4A serine proteases. The examiner cites Njoroge et. al. (Njoroge-I) as allegedly suggesting that significant challenges exist in developing HCV polymerase inhibition. (*Accounts of Chemical Research,* 2008, 41(1), 50-59) The examiner points to the passage in page 52, titled, "Challenges in discovering HCV protease inhibitors." The cited passage, however, does not support the rejection and does not suggest that *in vitro* and/or *in vivo* models cannot be relied upon to support a patent specification in this area, as mandated by the MPEP for enablement rejections involving *in vitro* and *in vivo* models. (See MPEP 2164.02).

The MPEP notes that, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition." *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. No such reason has been established by the examiner in the instant case. Furthermore, a rigorous or an invariable exact correlation between *in vivo* and *in vitro* models is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050,

224 USPQ 739, 747 (Fed. Cir. 1985): "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." (MPEP 2164.02). Since the prior art cited does not establish any evidence for the lack of correlation between *in vitro* and *in vivo* studies, the examiner has not established a *prima facie* case against enablement.

The instant application has established that the compounds herein are inhibitors of serine proteases, NS3 and NS4a, and that the compounds resulted in inhibition of viral replication in a cell based assay. (See page 234). Njoroge-I notes that, "Owing to the fact that the NS3-NS4A protease is playing a critical role in HCV viral replication, it has been viewed as an ideal target for the creation of new HCV therapy." (See page 52, Column 1, last paragraph). The applicants herein have identified that compounds herein have activity against the particular proteases that are critical for therapy. It is true that Njoroge-I further notes that their studies have not found any viable lead candidates even after the screening of four million compounds. (Page 52, column 1, last paragraph). This is the particular problem solved by the applicants in the instant application.

Njoroge-I notes the difficulty in identifying "lead drug candidates" for treating HCV. (Page 52, column 2, end of first paragraph; Page 57, column 2, paragraph 3). Njoroge-I does not state that active or useful compounds cannot be identified or that compounds possessing the disclosed activity will not also be useful *in vivo*. That is, the law quite clearly permits patenting compounds which may not possess the entire activity profile required to render the compound suitable to become a lead drug candidate. In fact, as of today, Njoroge has been granted at least 16 patents to HCV inhibitors on his work in this area, clearly patenting and asserting as enabled and useful *in vivo* those compounds which he apparently admits in this article did not present the entire activity profile required to render the compound suitable to become a "lead drug candidate." (See exhibit A). For example, the 7,253,160 patent, titled "Depeptidized inhibitors of hepatitis C virus NS3 protease" (Njoroge-II) claims methods for treating HCV infection.

(Claims 38-39, 42-43). Njoroge in the '160 patent performed spectrophotometric assays to elucidate the activity profile of compounds therein against serine proteases. The inventors in Njoroge-II apparently came to the conclusion that the compounds therein were useful for the treatment of HCV infection from *in vitro* studies. As such, one of skill in the art, including Njoroge, would have clearly concluded from *in vitro* studies showing activity against serine protease was indicative and correlated to *in vivo* activity as well.

Furthermore, the teachings of Njoroge-I, cited by the examiner, is directed to the identification of lead drug candidates. The factors involved in identifying a lead drug candidates are not necessarily the same as the requirements for enablement under section 112, first paragraph. For instance, identifying a lead candidate requires considerations such as pharmacokinetic profiles, toxicity, metabolic activity, the cost of manufacturing the drug, the ease at which it can be administered, the ability of deliver though multiple methods etc. These factors are different from the need to demonstrate pharmacological activity as required to be in compliance with the enablement requirement under section 112, first paragraph. The examiner appears to equate the enablement requirement under section 112, first paragraph with the difficulties involved in clinical development of drugs and assumes that enablement can only be found for compounds which have the profile of activities required for clinical development. Of course, the courts have repeatedly warned the USPTO that it is not a substitute for the FDA and patents are not limited to only approvable drug products. The examiner's conclusion that there are significant challenges in the discovery of HCV polymerase inhibitors and their use *in vivo* within the context of 35 USC 112 is misplaced and not what the art teaches at all.

The passage in which Njoroge-I states that the evaluation of *in vivo* efficacy is hampered by the lack of a convenient small animal model also discusses an alternative through which preclinical evaluation have been made. Njoroge-I notes that there are several clinical candidates including boceprevir for the treatment of HCV infection. The development of these clinical candidates indicate that the development of *in vivo* treatment for HCV infection is within the grasp of one of skill in the art despite the

absence of a convenient small animal model. Furthermore, there is no requirement that an applicant has to answer in a patent application the type of concerns that may arise in the clinical stage of using the invention. See, for example, *In re Brana*, 51 F.3d 1560,34 USPQ2d 1441 (Fed. Cir. 1995), and *In re Bundy*, 642 F.2d 430,209 USPQ 48, (CCPA 1981). Njoroge et. al. further notes that with the development of subgenomic replicon system, a severe combined immunodeficiency disease (SCID) mouse with chimeric human liver model, and chronically infected chimpanzee model, the preclinical evaluation of potential anti-HCV agents is currently possible. (Page 52, column 1, paragraph 2). As such, the methodology to perform *in vivo* studies is well within the grasp of one of skill in the arts. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). (See MPEP 2164.01).

The examiner alleges that the applicants have not established that the compounds of formula I will actually work *in vivo*. However, the applicants have noted that the compounds of the present invention exhibit potent inhibitory properties against the HCV NS3 protease. Furthermore, the applicants have presented exemplary assays in which the compounds of the present invention were successfully tested for anti-HCV effects. (Specification, pages 233-237). The court in *In re Marzocchi* noted that, "the first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad term analogy, it is of no importance." (439 F.2d 220, 169 U.S. P.Q. 367, CCPA 1971). Where a specification teaches the manner and process of making and using the invention, the specification must be taken as sufficient under §112, unless there is reason to doubt the truth of these statements. (See *In re Marzocchi*). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the

contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." (*In re Marzocchi*, 439 F.2d at 224, 169 USPQ at 370; MPEP 2164.04).

Since there is no established evidence of lack of correlation between *in vitro* and *in vivo* models and because the methods to perform preclinical evaluation of anti-HCV agents are well established there is no undue experimentation necessary to establish the activity as claimed herein. Njoroge's teachings, including the patents that have been granted to him enclosed herewith, do not contradict these conclusions. The withdrawal of the rejection of claims 66-70 under section 112, first paragraph is respectfully requested.

Claims Rejections – 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 70 and 74 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. Although the applicants respectfully disagree with the examiners rejection, in an effort to expedite the allowance of this case, applicants have herein cancelled claims 70 and 74. The withdrawal of the rejections of claims 70 and 74 under section 112, second paragraph is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue.

Applicants believe this response is filed timely. However, if necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 502807.

If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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Date: **16 April, 2008**